REMARKS

Status of the Claims

Written support for the amendments to the claims can be found in original claim 36. The amendments to the claims do not add prohibited new matter.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 51-56, 61, 67, and 69 have rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite as set forth on page 4 of the Office Action.

Without acquiescing to the merits of this rejection, Applicants have amended the claims to overcome this rejection. In view of Applicants amendments, Applicants believe that this rejection is moot and respectfully request that it be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 36-63 and 67-70 have rejected under 35 U.S.C. § 103(a) as allegedly being obvious over MacDonald in view of Rahman as set forth on page 6 of the Office Action.

Applicants respectfully submit that this rejection is in error. The claimed invention provides a treatment by administering a therapeutically effective amount of the cationic liposomes comprising paclitaxel without serious side effects (see [0014]), wherein a "therapeutically effective amount" is an amount which affects a disease such as cancer (see [0063]). Hence the claimed invention provides an effective and safe method of treating cancer.

Rahman relates to the problem of administering paclitaxel in a rapid and less toxic schedule (col. 2, l. 34-38). Rahman is completely silent on the problem of providing a therapeutically effective schedule for the administration of paclitaxel. Thus, one skilled in the art does not obtain any information from Rahman that would enable him to administer liposomes comprising paclitaxel with a predictable effectiveness.

McDonald only relates to liposomal compositions comprising paclitaxel. McDonald does not provide any relevant teaching on how to administer the disclosed liposomal compositions with predictable safety and effectiveness. The paragraph highlighted in the Office Action at page 11 only discloses a generic trial and error method of finding a suitable dosing for a drug without undue experimentation. The method disclosed by McDonald does not direct or suggest to one skilled in the art the dosing schedule of the claimed invention.

The Office Action (on page 11) further alleges that one skilled in the art would have to do no more than "perform routine experimentation" citing *In re Aller*. However *In re Aller* refers to

optimization of concentration or temperature. These parameters are optimized based on laboratory bench work. In contrast, the claimed invention provides a dosing schedule of a pharmaceutical composition with known toxic side effects, namely a parameter that cannot be simply deduced in a laboratory, but instead can only be arrived at through extensive clinical trials in human patients, trails which are both financially and chronologically costly. Moreover, Applicants submit that *In re Aller*, speaks to routine experimentation within a pre-established range. Neither Rahman or McDonald provides a range within which the claimed invention falls. To that end, the level of experimentation is far from routine, as Rahman and McDonald are silent on any dosing schedule.

Furthermore MPEP 2144.05 (II)(A) finds that a variation of parameters (like temperature and concentration in *In re Aller*) does not support patentability unless there is evidence that such parameters are critical. *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Applicants submit that the claimed dose schedule is highly critical for administering a drug in a save and effective manner, and is therefore not a peripheral parameter that ultimately does not effect the practice of the claimed invention.

As evidence, Applicants attach hereto a copy of a poster from the 34th ESMO (European Society for Medical Oncology) Multidisciplinary Congress (Berlin 2009) disclosing the use of liposomally encapsulated paclitaxel according to the pending claims in a clinical trial demonstrating effectiveness and safety of the claimed schedule. In short, single doses were 11 mg/m^2 (about 0.28 mg/kg), 22 mg/m^2 (about ca. 0.56 mg/kg) and 44 mg/m^2 (about 1.12 mg/kg), corresponding to a monthly dose of about 2.52 mg/kg, 5.04 mg/kg and 10.08 mg/kg. Accordingly, Applicants submit that the claimed invention is not obvious and cannot be derived from any combination of Rahman and McDonald. The claimed invention provides a critical dosing schedule that is effective and safe in treating humans, and one skilled in the art cannot arrive at the claimed schedule through any combination of these references or through routine experimentation. Applicants therefore respectfully request that this rejection be withdrawn.

Double Patenting

A. Claims 36-63 and 67-70 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 9, 11, 14, 18, and 20 of co-pending application 11/018,574.

B. Claims 36-63 and 67-70 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 13, 16, and 22 of co-pending application 12/300,448.

C. Claims 36-63 and 67-70 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 4, 5, and 9 of co-pending application 12/308,748.

Applicants note that these rejections are provisional based on a non-issued patent applications Accordingly, Applicants submit that a terminal disclaimer is required only if the claims continue to conflict and the currently pending claims are otherwise ready to be allowed. MPEP 804. Therefore, as this rejection is provisional in nature only, Applicants decline to address the merits at this point in prosecution.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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A phase II trial of cationic liposomal paclitaxel in combination with gemcitabine in patients with advanced pancreatic cancer

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Background:

- Treatment options for advanced pancreatic cancer are still unsatisfactory
- EndoTAG™-1 is a novel formulation of cationic liposomes carrying paclitaxel embedded in the liposome membrane (*Fig. 1*)
- Cationic liposomes bind and internalize at tumor endothelial cells after intravenous administration
- EndoTAG™-1 specifically displays antivascular and antiangiogenic activity

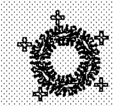
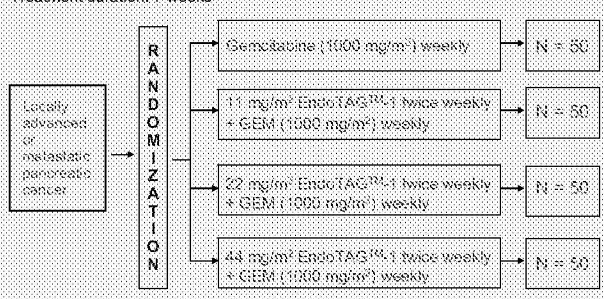


Figure 1. EndoTAG™-1

Methods:

- Patient Population:unresectable, locally advanced or metastatic pancreatic cancer (PC); N=200
- Open-label phase II study of first line combination treatment with weekly gemcitabine (G) (arm 1: G mono 1000 mg/m²) and twice weekly EndoTAG™-1 at 3 different dose levels (arms 2/3/4: 11/22/44 mg/m²).
- Treatment duration: 7 weeks



- **Treatment for 7 weeks (=1 cycle)**
- **Repeated treatment cycles in case of clinical benefit possible after amendment(Jan. 2007) for patients in EndoTAG™-1 groups**

Figure 2. Study design

Study population:

- 200 patients were randomized. Demographics and baseline characteristics are shown in *Table 1*.

	GEM mono (n=50)	GEM+EndoTAG™-1 11 mg/m² (n=50)	GEM+EndoTAG™-1 22 mg/m² (n=50)	GEM+EndoTAG™-1 44 mg/m² (n=50)
Median age (range)	59.5 (34-80)	63.0 (39-75)	61.0 (44-72)	62.5 (33-81)
Male patients	32 (64%)	34 (68%)	32 (64%)	33 (66%)
ECOG at baseline				
Grade 0	20 (40%)	22 (44%)	20 (40%)	18 (36%)
Grade 1	26 (52%)	22 (44%)	20 (40%)	[illegible]
Grade 2	4 (8%)	6 (12%)	10 (20%)	[illegible]
Current TNM staging				
Locally advanced	12 (24%)	8 (16%)	11 (22%)	12 (24%)
Metastatic	38 (76%)	42 (84%)	39 (78%)	38 (76%)

Table 1. Demographics and baseline characteristics of the study population (N=200)

Results:

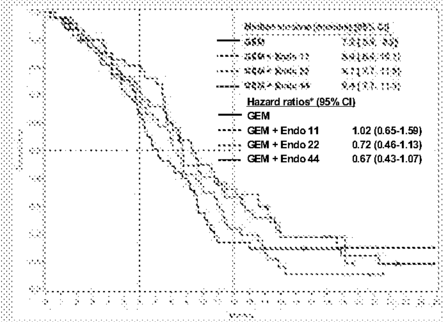


Figure 3. Kaplan-Meier plots for overall survival (OS)

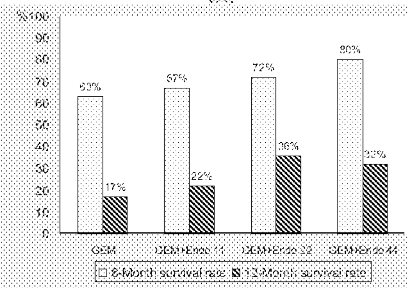


Figure 4. 6 and 12 month survival rates

	GEM mono (n=50)	GEM+EndoTAG™-1 11 mg/m² (n=50)	GEM+EndoTAG™-1 22 mg/m² (n=50)	GEM+EndoTAG™-1 44 mg/m² (n=50)
Any AE, N (%)	46 (92.0)	49 (98.0)	48 (96.0)	50 (100.0)
Number (%) of patients with AEs:				
Chills	4 (8.0)	11 (22.0)	18 (36.0)	26 (52.0)
Pyrexia	8 (16.0)	12 (24.0)	17 (34.0)	23 (46.0)
Neutropenia	17 (34.0)	12 (24.0)	13 (26.0)	23 (46.0)
Thrombocytopenia	7 (14.0)	9 (18.0)	14 (28.0)	22 (44.0)
Leukopenia	[illegible]	9 (18.0)	9 (18.0)	12 (24.0)
Anemia	11 (22.0)	9 (18.0)	8 (16.0)	20 (40.0)

Table 2. Relevant Adverse Events (any grade)

	GEM (n=50)	GEM+EndoTAG™-1 11 mg (n=50)	GEM+EndoTAG™-1 22 mg (n=50)	GEM+EndoTAG™-1 44 mg (n=50)
Any Grade 3/4 AE	27 (54.0)	[illegible]	[illegible]	[illegible]
Number (%) of patients with grade 3/4 AEs				
Neutropenia	[illegible]	6 (12.0)	[illegible]	11 (22.0)
Thrombocytopenia	1 (2.0)	4 (8.0)	[illegible]	[illegible]
Leukopenia	2 (4.0)	5 (10.0)	6 (12.0)	5 (10.0)
Anemia	2 (4.0)	1 (2.0)	[illegible]	6 (12.0)
GGT increased	[illegible]	10 (20.0)	11 (22.0)	7 (14.0)
ALAT increased	3 (6.0)	2 (4.0)	4 (8.0)	6 (12.0)
ASAT increased	1 (2.0)	1 (2.0)	[illegible]	2 (4.0)

Table 3. Grade 3/4 Adverse Events

Summary:

Study Population:
- Demographics were comparable across treatment groups (*Table 1*)
- 80% of patients had metastatic disease at enrollment (*Table 1*)
- 28 patients received repeated cycles of EndoTAG™-1 combination treatment (up to 8 cycles)

Efficacy:
- Substantial prolongation of overall survival in EndoTAG™-1 treatment groups compared to GEM mono group (*Fig. 3*)
- Higher 6 and 12 month survival rates in EndoTAG™-1 treatment groups (*Fig. 4*)
- Higher rate of tumor stabilization and prolongation of PFS in EndoTAG™-1 treatment groups (*data not shown*)

Safety:
- Marginal additive adverse reactions compared to GEM monotherapy
- Dose-dependent, manageable infusion-related reactions (grade 1/2 chills and pyrexia) and transient thrombocytopenia (*Tables 2, 3*)
- No evidence for clinically relevant organ toxicity or neurotoxicity
- No deaths possibly or probably related to study medication
- No indication for cumulative toxicity of EndoTAG™-1 in combination with GEM after repeated treatment cycles

Conclusion:

- EndoTAG™-1 combination therapy demonstrated a clear survival benefit in patients with advanced pancreatic cancer
- Favorable safety profile and positive benefit-risk ratio of EndoTAG™-1 in combination with gemcitabine
- Positive data from phase II clinical trial strongly supports further development of EndoTAG™-1 in advanced pancreatic cancer

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CT4001 Study Group

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